UNITED STATES DEPARTMENT OF COMMERCE
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
| | |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/030,061 | GILLSPIE ET AL. | |
| | Examiner | Art Unit | |
| | Dong Jiang | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6, and 8-27* is/are pending in the application.

4a) Of the above claim(s) *11-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-6, and 8-27* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s) _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

## DETAILED OFFICE ACTION

Applicant's election with traverse of Group I invention in Paper No. 11, filed on 26 April 2001 is acknowledged. The traversal is on the ground(s) that the method of using in Invention II is closely tied to the product of Invention I, and in order to do a complete search of the product, it would also be necessary to search the method as well, and therefore, there would be no serious burden in examining the method claims even though they are separately classified. This is not found persuasive because, contrary to applicants' assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other Group, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Applicant's attention is directed to MPEP 806.05.

The requirement is still deemed proper and is therefore made FINAL.

Currently claims 1-6 and 8-10 are under consideration.

***Double Patenting Rejections:***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 and 8-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, and 4 of U.S. Patent No. 6,207,641 B1. Although the conflicting claims are not identical, they are not patentably distinct from each

other for the following reasons. With respect to claims 1-5 and 10, claim 1 of the U.S. patent '641 is directed to a pharmaceutical composition comprising human IL-18 (SEQ ID NO:1), or homologous polypeptide thereof as an effective ingredient, wherein the homologous polypeptides has one amino acid residue replaced, or one amino acid residue added or deleted from the N- or C-terminus of SEQ ID NO:1. SEQ ID NO:6 of the instant case is 100% identical to SEQ ID NO:1 of the U.S. patent, and the protein of SEQ ID NO:6 and the variants (recited as "a functional equivalent thereof") are used as an effective ingredient in an osteoclastgenic inhibitory composition, wherein functional equivalents have one amino acid residue replaced, or one amino acid residue added or deleted from the N- or C-terminus of SEQ ID NO:6. Therefore, the pharmaceutical composition in claim 1 of the US patent includes the osteoclastgenic inhibitory composition in claims 1, 4, and 5 of the instant case as both have the same effective ingredient. Although the current claims recite a specific use for the composition, it does not alter the nature of the composition. Therefore, such limitation does not change the scope of the claimed composition. Additionally, SEQ ID NO:1 of the human IL-18 in '641 contains sequences of SEQ ID NOs:2-5 recited in claims 2 and 3 of the present application. The concentration limitation of 0.000002-100 w/w% in claim 10 is embraced within the range set forth in claim 1 of the U.S. patent, which is 0.000001-100 w/w%. Therefore, the conflicting claims are not patentably distinct from each other.

With respect to claims 8-9, in comparison, claims 3 and 4 of '641 are drawn to the pharmaceutical composition of claim 1, further comprising at least one member selected from the group consisting of stabilizers, adjuvants, excipients, diluents, and biologically-active substances (claim 3), and wherein the stabilizer is selected from the group consisting of serum albumin, gelatin, maltose, and trehalose (claim 4). The limitations of claims 8 and 9 of the present application are directed to stabilizers (claim 8), diluents, and excipients (claim 9), which are recited in the limitations of claims 3 and 4 of the U.S. patent. Therefore, the conflicting claims are not patentably distinct from each other.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 8-10 are also rejected under 35 U.S.C. 103(a) as being obvious over claim 1 of U.S. Patent No. 6,207,641 B1, for the same reasons addressed above.

The applied reference, '641, has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

***Objections and Rejections under 35 U.S.C. §112:***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 are indefinite for using the term "a functional equivalent". As the specification does not define the term with sequence specificity, the metes and bounds of the effective ingredient of the claims, therefore, cannot be unambiguously determined.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a an osteoclastgenic inhibitory composition, which comprises an IL-18 with SEQ ID NO:6, 7, or variants with Cys residues replaced as an effective ingredient, does not reasonably provide enablement for with claims to the composition which comprises "an functional equivalent" as an effective ingredient. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Enablement is not commensurate in scope with claims 1-3, 5 and 8-10, which contain an IL-18 with SEQ ID NO:6 or 7, or "an functional equivalent" thereof as an effective ingredient. The specification defines "functional equivalent(s)" as those wherein one or more amino acids in the amino acid sequence of IL-18 are replaced; added to or deleted from the N- and/or C-termini; inserted into or deleted from the internal sites or regions of the amino acid sequence of IL-18 (page 4). As there is no upper limit given on the number of amino acid changes, such "functional equivalent(s)" encompass a very broad range of molecules, which read on any or all molecules of the functional equivalent including other species of IL-18, and those without structural similarity to SEQ ID NO:6 or 7, and no structural limitation is actually required. For

instance, the claims would read on a molecule such as estrogen, or an IL-6 inhibitor (for example, soluble IL-6R or IL-6 neutralizing Ab), which have distinct sequences, and the same biological property (inhibition of osteoclastgenesis) in comparison to IL-18.

The specification discloses two wild-type sequences (SEQ ID NO:6 and 7) of IL-18, and the variants of SEQ ID NO:6 with cysteine substitutions (Experiments 3 and 4). Additionally, the disclosure indicates five consensus sequences (SEQ ID NO:1-5) within SEQ ID NO:6 and 7. The specification provides no clear direction or enough guidance to teach how to make a commensurate number of the claimed species with the desired biological property. Based upon the very limited number of disclosed species, and a single type of amino acid substitution, it is not predictable what essential structures are required for the protein to be functional, and it would require undue experimentation to determine such.

Given the reasons above, and the breadth of claims 1-3, 5 and 8-10, which encompass any or all molecules with osteoclastgenic inhibitory function, in light of the nature of the invention, which contains a protein with a specific sequence, the state of the prior art, the level of predictability in the art, and the amount of direction provided by the invention, it would require extensive undue experimentation for the skilled artisan to practice the invention as claimed.

Claims 1-3, 5 and 8-10 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The specification discloses *two* IL-18 amino acid sequences with particularity, the human and murine IL-18 with SEQ ID NO:6 and 7, respectively and and the variants of SEQ ID NO:6 with cysteine substitutions. The specification, therefore, provides merely a single type of amino

acid substitution, and no any other variants of IL-18 with amino acid deletion, or addition, or any other type of "functional equivalents" meeting the limitations of these claims were ever identified or particularly described.

The present claims 1-3, 5 and 8-10 encompass significant structural dissimilarity as compared to the exemplified IL-18 and the variants, and the limitations which are positively recited have not been shown to correlate with the biological activity required by these claims. A skilled artisan would not be able to reasonably expect, for example, that a molecule with the presence of short subsequences affording *ca.* 30% overall identity with SEQ ID NO:6 or 7 would correlate with the retention of biological properties characteristic of the human or murine IL-18 described in the disclosure. The Office therefore concludes that a single type of amino acid substitution of SEQ ID NO: 6, are not representative of all variants recited in claims 1-3, 5 and 8-10, and thus that the disclosure does not convey to those skilled in the art that the inventors were in possession of the genera of IL-18, variants or functional equivalents of IL-18 at the time the application was filed.

***Rejections Over Prior Art:***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-6, and 8-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Ushio et al., EP 0 712 931 A2.

Ushio discloses an amino acid sequence (SEQ ID NO:1) of human IFN-g-inducing factor (IGIF), which is now designated IL-18, and a pharmaceutical composition thereof (page 12). The referenced SEQ ID NO: 1 is identical to SEQ ID NO:6 of the present invention, and the polypeptide can be processed into compositions by mixing with a physiological-acceptable carrier, adjuvant, excipient, diluent, and/or stabilizer (page 12, lines 12-13), and in the form of a

liquid, paste or solid (page 12, line 10), which meet the limitations in claims 1-6, and 8-9. Further Ushio teaches that the concentration of the polypeptide in the composition is in an amount of 0.000001 – 100 w%w, which embraces the concentration set forth in claim 10 of the instant case, and therefore, anticipates claim 10.

Even though osteoclastgenic inhibitory effect of IL-18 was not assessed in the reference, the inhibition of osteoclastgenesis by IL-18 would be an inherent feature of a composition consisting of the same effective ingredient. Therefore, the cited reference clearly anticipates the instant claims.

Claims 1-3, 6, and 8 are also rejected under 35 U.S.C. 102(e) as being anticipated by Okamura et al., US 5,912,324.

Okamura discloses an amino acid sequence (SEQ ID NO:1) of murine IFN-g-inducing factor (IGIF), which is now designated IL-18, and has 100% sequence identity to SEQ ID NO:6 of the present invention. Further, Okamura teaches that to treat IFN-g susceptive diseases, IGIF are directly administered into mammals, for example, orally after formulated into appropriate forms, or by injection (column 7, lines 15-20), indicating a pharmaceutical composition of IL-18. Therefore, the reference anticipates claims 1-3, and 6.

Okamura does not teach explicitly IL-18 as "an osteoclastgenic inhibitory composition", and "comprises a pharmaceutically-acceptable carrier and an interleukin-18", or "further comprises a stabilizer", the referenced composition is not patentably distinct from the subject matter in the claims because effective ingredient of Okamura's composition is the same as that in the instant claims, and an osteoclastgenic inhibitory function would be an inherent feature of the composition consisting of the same effective ingredient. Additionally, Okamura teaches that the agents are administered after *formulated* into appropriated forms, or via injection, suggesting a pharmaceutical composition, which would indicate to the skilled artisan that the composition comprises pharmaceutically-acceptable carriers and/or stabilizers (can I say that ???). Accordingly, claim 8 is anticipated by the teachings of Okamura.

***Conclusion:***

No claim is allowed.

***Advisory Information:***

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

LORRAINE SPECTOR
PRIMARY EXAMINER

DJ
6/29/01